CLINICAL TRIALS IN PEDIATRIC HEAMATO-ONCOLOGY: DIFFERENT WAYS FOR HPS TO PARTICIPATE

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Disclosures

- No Conflict of interest

- Q1: do legal regulations apply equally for all kind of clinical trials?
- Q2: can all kind of haemato-oncological trial be put on the same level?
- Q3: are all drugs used in a clinical trial IMPs?

Learning objectives

After the session you should be able

- to outline the legal environment and discuss problems of administrations of drug clinical trials in children
- avoid getting lost in the jungle of legal environment of clinical trials in children

Why do trials need a pharmacist?

- According to ICH-GCP:

„ Where allowed/required, the investigator/institution may/should assign some or all of the investigator's/institution's duties for investigational product(s) accountability at the trial site(s) to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/institution."

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4_2016_1109.pdf

The pharmacist…

…maintains records about:

- Delivery
- Inventory
- Usage
- Disposition / Return of IMP
- Storage
- Blinding
- Reconstitution / Preparation

of the IMP

Why do Investigators like a pharmacist?

The pharmacist…

- Knows the IMP
- Knows technical pharmaceutical details
- Knows the local processes
- Knows other drugs (e.g. supportive or rescue medication, concomittant drugs,…)

> Interface between trial and clinical routine

Why do pediatric patients need a pharmacist?

- Pediatric population is
- 0 days to 18 years

- Every age needs certain adjustments
- (e.g. dose, infusion volume,…)

- High participation rate in clinical trials of children with cancer
  50% of children vs. 2-3% of adults (USA)

Caldwell et al.; The Lancet Volume 364, Issue 9436, 28 August–3 September 2004, Pages 803-811

Industry-driven trials

> Marketing authorisation

- Sponsor - pharmaceutical company
  provides requirements on

- Documentation
- Handling instructions
- Processes

> can „easily“ be used

Industry-driven trials

- Challenges for the pharmacist:

- Sponsor requires very consistent standards for all sites which may not comply with local standards
- Local availability of comparator, protocols, auxiliary material (e.g. infusion bags in pre-specified volume)
- Slow recruitment
- PK-Analyses <> narrow time windows

Example

- ALL relapsed, refractory
- Site activation: september 2015
- 8 drugs
- 4 protocols (induction, consolidation 1 and 2, experimental arm)

- 0 Patients enrolled at our site

  Still waiting…

Investigator-driven trials

- cover additional therapeutic need
- aquire new information (e.g. biomarker)

- > new protocols
- > new sequences/combinations of therapies

Investigator-driven trials

Sponsor

- national/international working group
- single physician

- provides the study protocol

Investigator-driven trials

Challenges for the pharmacist:

- less specification by sponsor for organizational and/logistical details > more individual responsibilty
- local availability of drugs (e.g. multicentric, multinational working groups)
- use of „off-label“ drugs in well established protocols
- treatment „according to study-protocol“ but patient is not enrolled in the trial
- formulation

Investigator-driven trials

- GCP is still applicable!

Clinical trials for children with cancer in Europe – Still a long way from harmonisation: A report from SIOP Europe

- 70% of children newly diagnosed with cancer would enter phase III clinical trial.

- The bureaucratic workload of trial activation is much too high for rare diseases like childhood cancer.

K. Pritchard-Jones; **European Journal of Cancer** Volume 44, Issue 15, October 2008, Pages 2106-2111

Table 1 – Key issues for paediatric cancer trials in relation to the EU CTD

Issue	Experience of European paediatric study groups running investigator-led ('non-commercial') trials in childhood cancers
Definition of an interventional clinical trial	'Standard of care' regimens often include medicines used 'off label' Variation in acceptance by national regulatory authorities of such use as 'background medicine' or whether it falls outside the definition of an 'interventional clinical trial'
Sponsorship	National variation in whether a single European sponsor is required or a national co-sponsorship arrangement is accepted Complex contractual negotiations required between partners
Insurance and Indemnity	Large variation in costs and in whether 'no fault' indemnity is required Insurance costs increased 100-fold with no perceptible change in risks between consecutive trials of the same study group Premiums may be paid by fundraising efforts of childhood cancer parents' associations
Definition of an IMP	Hugely variable for use of old drugs with no or limited paediatric information in their marketing authorisations IMP definition has major impact on bureaucracy of pharmaco-vigilance
Pharmaco-vigilance	Hugely bureaucratic with no noticeable improvement in patient safety (which was in any case very good in childhood cancer trials) National variation in onward reporting requirements for SUSARs when drug is used in more than one trial Inconsistency in inspection findings of regulatory processes for the same trial
Sponsor obligation to provide free drug	Large national variations in how this is absorbed into national health insurance schemes or whether this must be paid for by sponsor Required for IMPs, whose definition is also variable
Drug formulations adapted for children	Lack of appropriate formulations for young children for many oral anti-cancer drugs Strict definition of 'manufacturing' excludes young children from some clinical trials when no appropriate formulation exists
Ethical considerations	Ethical committees need appropriate expertise to evaluate appropriateness of new drug trials in children Timelines to receive the 'single' national ethical approval highly variable Institutions have created other hurdles to opening a trial, variably labelled 'R & D' approval

K. Pritchard-Jones; **European Journal of Cancer** Volume 44, Issue 15, October 2008, Pages 2106-2111

Regulatory

- ICH-GCP Guidelines

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4_2016_1109.pdf

Describes the responsibilities of all participants in the conduct of clinical trials.

"The investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. (…)"

Regulatory

- EudraLex Volume10, Clinical Trials Guideline: https://ec.europa.eu/health/documents/eudralex/vol-10_en

- Contains guidance documents applying to clinical trials:
- Chapter III - Quality of the investigational medicinal product
- Good manufacturing practice for investigational medicinal products
- Guidance on Investigational Medicinal Products (IMPs) and "non investigational medicinal products" (NIMPs)
- https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/imp_03-2011.pdf

NIMP

- NIMPs are medicinal products that fall within Article 3(3) of Directive 2001/83/EC, while not falling within the definition of IMP as defined in Article 2(d) of Directive 2001/20/EC

NIMP

- Rescue medication
  - e.g. treatment of anticipated adverse events
- Medicinal products used to assess end-points in the clinical trial
  - e.g. PET-tracer
- Concomitant medicinal products systematically prescribed to the study patients
  - e.g. antiemetic treatment
- Background treatment
  - e.g. standard of care
- Challenge agents
  - e.g. prick-test

Regulation (EU) No 536/2014

- https://ec.europa.eu/health/documents/eudralex/vol-10_en#fragment1

- Currently under revision

Regulatory

- Paediatric investigation plan, PIP: http://www.ema.europa.eu
- *Home > Human regulatory > Research and development > Paediatric medicines >Paediatric investigation plans*

- Development plan aimed at ensuring that the necessary data are obtained through studies in children, to support the authorisation of a medicine for children. All applications for marketing authorisation for new medicines have to include the results of studies as described in an agreed PIP

Pediatric Investigation Plan (PIP)

- includes a description of the measures to be carried out in children with the medicine;
- describes the measures to adapt the medicine's formulation to make its use more acceptable in children, such as use of a liquid formulation rather than large tablets;
- covers the needs of all age groups of children, from birth to adolescence;
- defines the timing of measures in children compared to adults.

Pediatric age groups

- Preterm newborn infants
- Term newborn infants (0 to 27 days)
- Infants and toddlers (28 days to 23 months)
- Children (2 to 11 years)
- Adolescents (12 to 16-18 years - dependent on region)

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E11/Step4/E11_Guideline.pdf

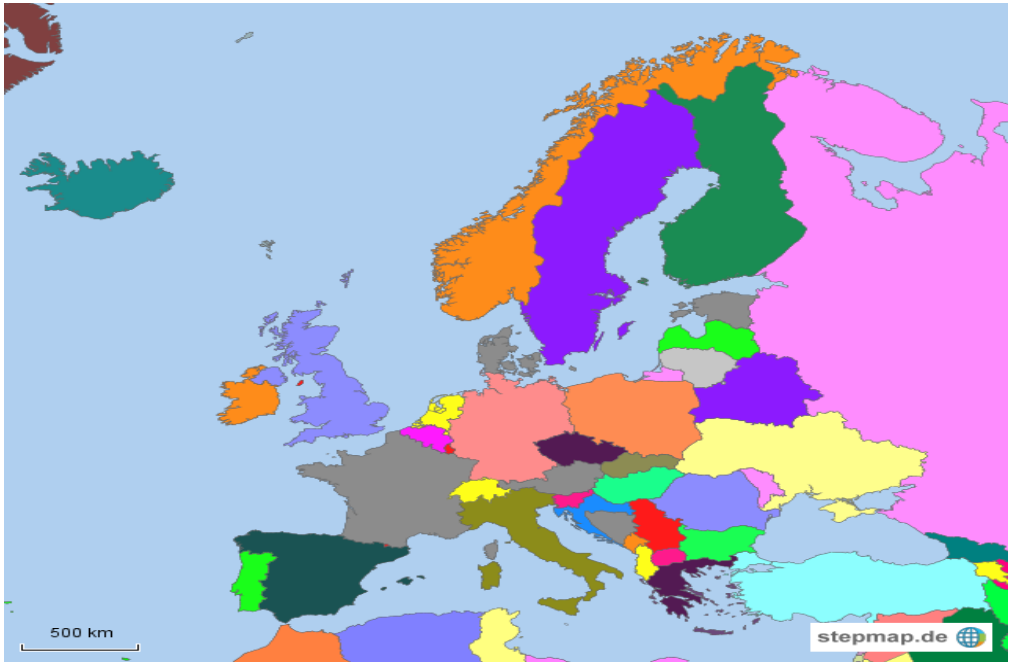
Regulatory

- Paediatric Committee, PDCO
- http://www.ema.europa.eu
- Home > Committees > PDCO

- Responsible for agreeing or refusing the PIP.

Regulatory

- EU-Legislation <> national regulatory



http://www.stepmap.de/landkarte/europa-139431

Regulatory

- Regulatory <> local circumstances

Wien.orf.at

- Q1: do legal regulations apply equally for all kind of clinical trials?

  YES

- Q2: can all kind of haemato-oncological trial be put on the same level?

  NO

- Q3: are all drugs used in a clinical trial IMPs?

  NO

To summarize

- Know your local processes
- Know the protocol‘s requirements
- Know your locally applicable laws

Thank you for your attention